

How to evaluate the calibration of a disease risk prediction tool.

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SUMMARY

To evaluate the calibration of a disease risk prediction tool, the quantity E/O , i.e., the ratio of the expected number of events to the observed number of events, is generally computed. However, because of censoring, or more precisely because of individuals who drop out before the termination of the study, this quantity is generally unavailable for the complete population study and an alternative estimate has to be computed. In this paper, we present and compare four methods to do this. We show that two of the most commonly used methods generally lead to biased estimates. Our arguments are first based on some theoretic considerations. Then, we perform a simulation study to highlight the magnitude of the previously mentioned biases. As a concluding example, we evaluate the calibration of an existing predictive model for breast cancer on the E3N-EPIC cohort.

KEY WORDS : risk prediction tool, calibration, goodness-of-fit, censoring.

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1. INTRODUCTION

Researchers, physicians, as well as the general public, are focusing increasingly on statistical models designed to predict the occurrence of a disease. The first corresponding model – the Framingham Coronary Risk Prediction Model published in 1976 [13] – was aimed at predicting the individual’s risk of developing heart disease. Modified versions of this primary model are now widely used by physicians to make decisions on prevention and treatment strategies. From the late 1980’s, researchers published prediction models for the absolute risk of breast cancer [2], [8], [16], and some prediction tools dealing with other types of cancer have begun to appear in the literature over recent years [1], [17]. In a workshop held in 2005, Freedman et al. [7] already pointed out the growth of both the number of cancer risk prediction tools and the need to ensure that they are rigorously evaluated.

Two main criteria, discrimination and calibration, are usually retained for evaluation. Other criteria may be retained for particular purposes, see [9] for some relevant examples. Discrimination measures the ability to segregate the individuals into two groups, those who will develop the disease, and those who will not. It is often evaluated by the concordance statistic, which is also the area under a receiver operating characteristic (ROC) curve. Calibration – our concern here – measures the ability to predict the number of events in the population of interest \mathbb{S} , usually over a t_0 -year period, $t_0 > 0$: it measures the *goodness-of-fit* of the model. Calibration is commonly evaluated by comparing the observed number of events with the number of events expected to occur within the t_0 -year period [14], [15]. By summing the estimated t_0 -year risks over all individuals belonging to a given representative sample \mathbb{S}_n of the population \mathbb{S} , we get the expected number of cases E . Considering in its turn the number O of cases observed in \mathbb{S}_n over the t_0 -year period, the E/O ratio provides an estimator of the theoretical quantity \mathcal{E}/\mathcal{O} that would be obtained by evaluating the considered model on the whole population \mathbb{S} , assumed to be infinite (in this asymptotic setting, \mathcal{E} and \mathcal{O} would stand for rates rather than numbers). A well calibrated model on \mathbb{S} would have a theoretic \mathcal{E}/\mathcal{O} equalling 1. Thus, the E/O ratio is usually statistically compared to one to definitely assess the model calibration.

However, due to either administrative reasons (the patient was followed until the end of the study but did not develop the disease by that date) or the *dropping out* phenomenon (including both "pure" loss of follow-up and death for reasons other than the considered disease) data are censored in most epidemiologic studies. This implies that the t_0 -year status regarding the disease is unknown for some individuals, and that the only available information for these individuals is that they did not develop the disease after z years of follow-up, with $0 < z < t_0$. In other words, the number of cases which would have occurred in the population \mathbb{S}_n over the t_0 -year period is unknown, because of the individuals who dropped out before t_0 years of follow-up. To get round this issue, various methods have been proposed and applied to provide estimators alternative to the *unobserved E/O* ratio. However, as will be shown later, most of these methods generally lead to biased estimates. In the following Section 2, we provide the derivation of four methods. For each of them we explain its principle as well as its potential inaccuracy from a theoretical point of view. The confidence bands associated with each method are also presented. Then, in Section 3, a comparison between the four methods is performed on simulated data. Finally we compare these methods on a real sample, the E3N-EPIC cohort, in which we evaluate one of the Nurses Health Study based breast cancer prediction tools [16] (see Section 4). These examples support our assertion that two most commonly used methods lead to potentially highly biased estimates.

2. METHODS

2.1. Notations

Some notations will be of particular interest to describe the various methods that have been (or can be) used to evaluate calibration.

Let Y be the random variable of interest (in most cases, Y will stand for the delay between the inclusion in the study and the occurrence of the considered disease), and C the censoring variable. The observed variables will be denoted by $Z = \min(Y, C)$ and $\delta = \mathbb{I}\{Y \leq C\}$, where $\mathbb{I}_{\mathcal{S}}$ equals 1 if the condition \mathcal{S} is true and 0 otherwise (i.e., here, δ equals 1 if $Y \leq C$,

and 0 otherwise). We fix $t_0 > 0$ and consider the evaluation of a t_0 -year risk prediction tool P_{t_0} on a given population \mathbb{S} . Assume a representative sample $\mathbb{S}_n = \{1, \dots, n\} \subset \mathbb{S}$, $n \geq 1$, is at our disposal. In this setting, our aim is to estimate the theoretical \mathcal{E}/\mathcal{O} ratio (relative to P_{t_0} on \mathbb{S}) on the sample \mathbb{S}_n . For every individual $i \in \mathbb{S}_n$, denote by z_i his observed time of follow-up, and $e_i = e_i(t_0)$ his expected risk according to P_{t_0} . Throughout, we will assume that $t_0 \leq \max_{i \in \mathbb{S}_n} z_i$. Further introduce the random variable $O_i = \mathbb{I}\{Y_i \leq t_0\}$ (i.e., O_i equals one if $Y_i \leq t_0$ and 0 otherwise), and set o_i for the realisation of O_i , $i = 1, \dots, n$.

We will denote by $\mathbb{S}_{n,ks}$ the group consisting of individuals for whom the status regarding the disease after t_0 years of follow-up is known. They will be referred to hereafter as 'known t_0 -status individuals'. This group consists of

1. individuals who developed the disease before t_0 years of follow-up ($y_i \leq c_i$, $z_i \leq t_0$ and $o_i = 1$ for these individuals);
2. individuals who developed the disease after t_0 years of follow-up ($y_i \leq c_i$, $z_i \geq t_0$ and $o_i = 0$ for these individuals);
3. individuals who did not develop the disease and were followed-up at least t_0 years ($c_i \leq y_i$, $z_i \geq t_0$ and $o_i = 0$ for these individuals).

Here and elsewhere, y_i [resp. c_i] stands for the realisation of the random variable Y_i [resp. C_i]. Similarly, we will denote by $\mathbb{S}_{n,uks}$ the group consisting of individuals for whom the status is unknown: for these 'unknown t_0 -status individuals', $c_i \leq y_i$, $z_i \leq t_0$, so O_i is unobserved and o_i is unknown.

Note that the rate of unknown t_0 -status individuals increases as t_0 increases. Therefore, the size of $\mathbb{S}_{n,uks}$ relatively to that of $\mathbb{S}_{n,ks}$ increases as t_0 increases. In addition, $\mathbb{S}_{n,ks}$ as well as $\mathbb{S}_{n,uks}$ are unrepresentative with respect to the whole population \mathbb{S}_n , as generally,

$$\begin{aligned} \mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_{n,ks}) &\neq \mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_n) \\ \text{and } \mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_{n,uks}) &\neq \mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_n). \end{aligned} \quad (1)$$

More precisely, one can see that $\mathbb{S}_{n,ks}$ overrepresents cases with respect to \mathbb{S}_n , i.e.,

$$\mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_{n,ks}) \geq \mathbb{P}(Y_i \leq t_0 | i \in \mathbb{S}_n). \quad (2)$$

This is the main reason why, to derive inference on \mathbb{S} in the presence of censoring, typical tools (e.g., the Kaplan-Meier estimate when estimating the unconditional probability of developing the disease) are required to ensure unbiased estimates.

Before presenting the four methods aimed at evaluating the calibration of P_{t_0} on \mathbb{S} , some additional notations are needed. Denote by n_{ks} [resp. n_{uks}] the number of individuals belonging to $\mathbb{S}_{n,ks}$ [resp. $\mathbb{S}_{n,uks}$]. Obviously, we have $n = n_{ks} + n_{uks}$ (since $\mathbb{S}_{n,ks} \cup \mathbb{S}_{n,uks} = \mathbb{S}_n$ and $\mathbb{S}_{n,ks} \cap \mathbb{S}_{n,uks} = \emptyset$). The following quantities will be of particular interest in the sequel. Introduce

$$\begin{aligned} E_{\mathbb{S}_n} &= \sum_{i \in \mathbb{S}_n} e_i; & E_{\mathbb{S}_{n,ks}} &= \sum_{i \in \mathbb{S}_{n,ks}} e_i; & E_{\mathbb{S}_{n,uks}} &= \sum_{i \in \mathbb{S}_{n,uks}} e_i; \\ O_{\mathbb{S}_n} &= \sum_{i \in \mathbb{S}_n} O_i; & O_{\mathbb{S}_{n,ks}} &= \sum_{i \in \mathbb{S}_{n,ks}} O_i; & O_{\mathbb{S}_{n,uks}} &= \sum_{i \in \mathbb{S}_{n,uks}} O_i. \end{aligned}$$

Note that the " O " terms are random and possibly unobserved (in particular, $O_{\mathbb{S}_n}$ and $O_{\mathbb{S}_{n,uks}}$ are unobserved) whereas the " E " terms are non-random and known. This is classical in evaluation studies where inference is made given the sample, which ensures that e_i is non-random for $i = 1, \dots, n$.

Since $O_{\mathbb{S}_n}$ is unobserved, $E_{\mathbb{S}_n}/O_{\mathbb{S}_n}$ cannot be used to estimate the theoretical \mathcal{E}/\mathcal{O} ratio. We present four methods to get round this issue in the following paragraphs.

2.2. Method M_0

In some validation studies [14],[15], the evaluation of the calibration is restricted to $\mathbb{S}_{n,ks}$, and the quantity \mathcal{E}/\mathcal{O} is estimated by

$$\mathcal{R}_{0,n} = E_{\mathbb{S}_{n,ks}}/O_{\mathbb{S}_{n,ks}}. \quad (3)$$

However, in view of (1)–(2), if a model has to be evaluated on \mathbb{S}_n , a lot of attention has to be paid when the validation is performed on $\mathbb{S}_{n,ks}$: if the score is well calibrated on \mathbb{S} (and then on \mathbb{S}_n), then the expectation of the $E_{\mathbb{S}_{n,ks}}/O_{\mathbb{S}_{n,ks}}$ ratio does not equal 1. In fact, it can even be shown that this expectation is less than 1, since the known t_0 -status group $\mathbb{S}_{n,ks}$ overrepresents cases with respect to \mathbb{S}_n and \mathbb{S} (see (2) above and (11) below).

2.3. Method M_1

Another method, evaluating the calibration on the whole population \mathbb{S}_n , can be found in the literature (see, for instance, [3]). The underlying idea is that although $O_{\mathbb{S}_n}$ is not at our disposal, $O_{1,\mathbb{S}_n} = \sum_{i \in \mathbb{S}_n} \mathbb{I}\{Y_i \leq \min(z_i, t_0)\}$ is. Then, setting

$$E_{1,\mathbb{S}_n} = \sum_{i \in \mathbb{S}_n} e_i(\min(t_0, z_i)), \quad (4)$$

the estimate of \mathcal{E}/\mathcal{O} is computed as follows

$$\mathcal{R}_{1,n} = E_{1,\mathbb{S}_n}/O_{1,\mathbb{S}_n} = E_{1,\mathbb{S}_n}/O_{\mathbb{S}_n,ks}. \quad (5)$$

Note that $e_i(\min(t_0, z_i)) = e_i(t_0)$ only for individuals i who were still disease-free after t_0 years. For all other individuals (i.e., the individuals belonging to $\mathbb{S}_{n,uks}$, plus the individuals belonging to $\mathbb{S}_{n,ks}$ for whom $o_i = 1$), we have $e_i(\min(t_0, z_i)) = e_i(z_i) \leq e_i(t_0)$.

To see why this method is inappropriate, we present a simple example. Assume a database of 10,000 individuals followed over a 5-year period (with no dropping-out) is at our disposal. Further suppose that the risk of the considered disease is uniform over the 5-year period, such that $\mathbb{P}(Y \leq t) = t/100$, for all $t \leq 5$. Then about 100 cases are likely to be observed each year. Assume 100 cases are observed each year (giving 500 cases observed overall) and the evaluation of the prediction tool $P_t = t/100$, for all $t \leq 5$, is under study. All the 9,500 individuals who remained free from disease after the 5-year period contribute to 5% in the calculus of E_{1,\mathbb{S}_n} . On the other hand, all the individuals who developed the disease within the first year of follow-up contribute to (at most) 1%, those who developed the disease within the second year of follow-up to 2%, and so on. Therefore, according to M_1 , the number of expected cases is (at most)

$$100 \times 1\% + 100 \times 2\% + 100 \times 3\% + 100 \times 4\% + 100 \times 5\% + 9,500 \times 5\% = 490,$$

in such a way that $\mathcal{R}_{1,n} = 0.98$! Obviously, the bias is more severe when the disease prevalence is high.

2.4. Method M_2

An easy way to correct the aforementioned bias pertaining to M_1 exists. In fact, $O_{\mathbb{S}_{n,ks}}$ is known and only $O_{\mathbb{S}_{n,uks}}$ is unknown. Following the idea of M_1 , however, $O_{1,\mathbb{S}_{n,uks}} = \sum_{i \in \mathbb{S}_{n,uks}} \mathbb{I}\{Y_i \leq \min(z_i, t_0)\} (= \sum_{i \in \mathbb{S}_{n,uks}} \mathbb{I}\{Y_i \leq z_i\} = 0)$, and thus, $O_{2,\mathbb{S}_n} = O_{\mathbb{S}_{n,ks}} + O_{1,\mathbb{S}_{n,uks}}$ are known. Therefore, setting

$$E_{2,\mathbb{S}_n} = \sum_{i \in \mathbb{S}_{n,ks}} e_i(t_0) + \sum_{i \in \mathbb{S}_{n,uks}} e_i(z_i), \quad (6)$$

a new estimate of \mathcal{E}/\mathcal{O} is given by

$$\mathcal{R}_{2,n} = E_{2,\mathbb{S}_n}/O_{2,\mathbb{S}_n} = E_{2,\mathbb{S}_n}/O_{\mathbb{S}_{n,ks}}. \quad (7)$$

Concretely, in (6), the individuals who developed the disease before t_0 years of follow-up contribute to $e_i(t_0)$ while they contribute to $e_i(z_i)$ in (4) (keep in mind that $e_i(z_i) \leq e_i(t_0)$ because $z_i \leq t_0$ for such individuals). Comparing the estimates provided by M_1 and M_2 , it is easily derived that

$$\mathcal{C}_1(t_0) = \frac{\mathcal{R}_{2,n}}{\mathcal{R}_{1,n}} = 1 + \frac{\sum_{i \in \mathbb{S}_{n,ks}} \delta_i \{e_i(t_0) - e_i(z_i)\}}{O_{\mathbb{S}_{n,ks}}} \geq 1. \quad (8)$$

Note that, to our knowledge, M_2 has never been used so far, although it provides a simple and practical way to improve M_1 . However, it is not clear whether $\mathcal{R}_{2,n}$ is unbiased or not: the explicit expression of the expectation of $\mathcal{R}_{2,n}$ (or $1/\mathcal{R}_{2,n}$) can not be easily derived. Moreover, there exists a drawback common to both M_1 and M_2 : using either method, the evaluation of a crude t_0 -year risk score can not be performed. In fact, some of the e_i 's involved in the calculation of E_{1,\mathbb{S}_n} and E_{2,\mathbb{S}_n} are attached to a t_0 -year period, while others are attached to a z_i -year period. The main problem arises when calibration is adjusted for percentiles of predicted risk (which is quite common in evaluation studies), and is due to the fact that the e_i 's are not comparable. In this adjusted setting, the estimation of the e_i 's distribution, and then the derivation of their percentiles, becomes hazardous. Similar problems also arise when calibration is adjusted for risk factors (such as age at inclusion or personal history of the disease). Therefore, M_2 should not be used when adjusted calibration has to be evaluated.

2.5. The method M_3

Keep in mind that in the absence of dropping-out, the quantity $E_{\mathbb{S}_n}/O_{\mathbb{S}_n}$ provides a suitable estimate of \mathcal{E}/\mathcal{O} . The problem in the presence of dropping-out arises from the fact that $O_{\mathbb{S}_n}$ is unknown. However, a natural candidate to replace $O_{\mathbb{S}_n}$ is defined as follows,

$$\widehat{O}_{\mathbb{S}_n} = nK_n(t_0), \quad (9)$$

where $K_n(t_0)$ is the Kaplan-Meier estimate of $\mathbb{P}(Y \leq t_0)$ on \mathbb{S}_n . Using this [4], an estimate of \mathcal{E}/\mathcal{O} can be given by

$$\mathcal{R}_{3,n} = \frac{E_{\mathbb{S}_n}}{\widehat{O}_{\mathbb{S}_n}}. \quad (10)$$

Note that since $K_n(t_0) \rightarrow \mathbb{P}(Y \leq t_0)$ almost surely as $n \rightarrow \infty$, for any $t_0 \leq \max_{i \in \mathbb{S}_n} z_i$ [18], it is easily derived that $\mathcal{R}_{3,n}$ is asymptotically unbiased.

Through this theoretical description of the various methods, we showed that $\mathcal{R}_{0,n}$ and $\mathcal{R}_{1,n}$ provide biased estimates. Moreover, the asymptotic unbiasedness was established for $\mathcal{R}_{3,n}$ but not for $\mathcal{R}_{2,n}$, suggesting that $\mathcal{R}_{3,n}$ is the most reliable estimate of the \mathcal{E}/\mathcal{O} ratio. Moreover, $\mathcal{R}_{3,n}$ is intuitively the most appealing estimator because it takes into account all the information available after t_0 years of follow-up. These statements will be confirmed by the simulation studies performed in Section 3.

2.6. Some complements

Some additional properties of the various methods merit presentation.

2.6.1. The inadmissibility of M_0 Comparing $\mathcal{R}_{0,n}$ and $\mathcal{R}_{3,n}$ gives insight into the magnitude of the bias pertaining to M_0 . Under the assumption of independence between the vector of covariates and the censoring variable, it can be shown that

$$\mathcal{C}_0(t_0) = \frac{\mathcal{R}_{3,n}}{\mathcal{R}_{0,n}} = \frac{E_{\mathbb{S}_n}/\widehat{O}_{\mathbb{S}_n}}{E_{\mathbb{S}_{n,ks}}/O_{\mathbb{S}_{n,ks}}} \approx \frac{F_{n_{ks}}(t_0)}{K_n(t_0)} = \tilde{\mathcal{C}}_0(t_0), \quad (11)$$

where $F_{n_{ks}}(t_0)$ is the empirical distribution function on $\mathbb{S}_{n,ks}$, i.e., the standard estimate of the probability of developing the disease on $\mathbb{S}_{n,ks}$. See Appendix for the proof of (11).

Since $K_n(t_0) \leq F_{n_{ks}}(t_0)$, almost surely for n large enough, we have $\mathcal{C}_0(t_0) \geq 1$. For instance, set $\mathcal{Z} = \max_{i \in \mathbb{S}_n} z_i$, and select $t_0 = \mathcal{Z}$. In this particular example, all the cases belong to $\mathbb{S}_{n,ks}$; non-cases do not. Thus, $F_{n_{ks}}(\mathcal{Z}) = 1$, while $K_n(\mathcal{Z}) \ll 1$ (typically, $K_n(\mathcal{Z})$ does not exceed 0.2), and $\mathcal{C}_0(\mathcal{Z})$ becomes high. Even if this case is somewhat extreme, it highlights the inadmissibility of M_0 , which is however among the most widely used of methods.

2.6.2. Confidence intervals In order to conclude whether a given prediction tool is well calibrated on \mathbb{S} or not, confidence intervals are generally needed. When the estimation of \mathcal{E}/\mathcal{O} is based on M_0 , M_1 or M_2 , such intervals can be calculated using the Poisson variance for the logarithm of the observed number of cases [15]. Namely, for $j = 0, 1, 2$,

$$\text{CI}_{j,n,95\%}(\mathcal{E}/\mathcal{O}) = \left[\mathcal{R}_{j,n} \exp \left(\pm 1.96 \sqrt{1/O_{\mathbb{S}_{n,ks}}} \right) \right]. \quad (12)$$

Note that, since M_0 and M_1 lead to biased estimates of the quantity \mathcal{E}/\mathcal{O} , the above formula may only be correct for $j = 2$ (if, eventually, $\mathcal{R}_{2,n}$ turns out to be unbiased).

On the other hand, in the case of M_3 , a log-transformation can be coupled with the delta-method, giving

$$\text{Var} \left[\log \left(\frac{E_{\mathbb{S}_n}}{\hat{O}_{\mathbb{S}_n}} \right) \right] = \frac{\sigma_{n,t_0}^2}{K_n^2(t_0)},$$

where σ_{n,t_0}^2 is the Greenwood variance [12] of the Kaplan-Meier estimate evaluated at t_0 . The corresponding confidence interval is given by

$$\text{CI}_{3,n,95\%}(\mathcal{E}/\mathcal{O}) = \left[\mathcal{R}_{3,n} \exp \left(\pm 1.96 \frac{\sigma_{n,t_0}}{K_n(t_0)} \right) \right]. \quad (13)$$

3. SIMULATION STUDY

A simulation study was performed to check that $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$ were better estimates of the \mathcal{E}/\mathcal{O} ratio than $\mathcal{R}_{1,n}$ and $\mathcal{R}_{0,n}$, and to compare $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$.

We considered the case where $Y \rightsquigarrow \mathcal{U}(0, \lambda)$, for a given $\lambda > t_0$, i.e., Y was uniformly distributed on the interval $[0, \lambda]$. This ensured that $\mathbb{P}(Y \leq t) = t/\lambda$, for all $0 \leq t \leq \lambda$. Note that the higher the rate $1/\lambda$, the higher the “prevalence of the disease”, and therefore, the higher the bias of $\mathcal{R}_{1,n}$ is expected to be (see Section 2.3). For the censoring variable, we chose $C \rightsquigarrow \mathcal{U}(0, \omega_\lambda)$,

for a given $\omega_\lambda > 0$. To allow the rate of unknown t_0 -status individuals to vary, we selected various values of ω_λ , depending on the rate $1/\lambda$. We also considered the case with no censor (and therefore with no unknown t_0 -status individuals) to check that M_0 , M_2 and M_3 provided the same estimates in this case.

Given $n \geq 1$, samples (Y_1, \dots, Y_n) and, if appropriate, (C_1, \dots, C_n) were simulated. From these samples, we generated the “observed” sample $((Z_1, \delta_1), \dots, (Z_n, \delta_n))$, where, as usual, $Z_i = \min(Y_i, C_i)$ and $\delta_i = \mathbb{I}\{Y_i \leq C_i\}$. The population $\mathbb{S}_n = \{1, \dots, n\}$ could then be split into $\mathbb{S}_{n,ks}$ and $\mathbb{S}_{n,uks}$, making the calculation of $O_{\mathbb{S}_{n,ks}}$ and $O_{\mathbb{S}_{n,uks}}$ possible. Moreover, the Kaplan-Meier estimate could be calculated on our samples, enabling us to compute $\hat{O}_{\mathbb{S}_n}$. Finally, the terms $E_{\mathbb{S}_n}$, $E_{\mathbb{S}_{n,ks}}$, E_{1,\mathbb{S}_n} and E_{2,\mathbb{S}_n} , and then $\mathcal{R}_{0,n}$, $\mathcal{R}_{1,n}$, $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$, were computed using the formula $e_i(t_0) = t_0/\lambda$ and $e_i(z_i) = z_i/\lambda$, and the corresponding confidence intervals were constructed making use equations (12) and (13). Note that, given the way the expected number of cases was calculated, the underlying prediction tool should be well calibrated, and $\mathcal{R}_{j,n}$ should be close to one if the method M_j , $j = 0, 1, 2, 3$, provided unbiased estimates of the \mathcal{E}/\mathcal{O} ratio.

In every example, we selected $n = 20,000$ and $t_0 = 10$. We repeated the procedure described above 1,000 times, computing (i) the mean for each of the $\mathcal{R}_{j,n}$, $j = 0, 1, 2, 3$, (ii) the mean width of the corresponding confidence interval and (iii) the proportion of confidence intervals including the value 1 (which is an estimate of the covering probability of the confidence interval).

We selected $\lambda = 100$, $\lambda = 200$ and $\lambda = 400$, and in each case, we selected three values of ω_λ such that there was 5%, 10% and 20% of unknown 10-year status individuals (plus the case with no censor at all): this resulted in $3 \times 4 = 12$ simulation designs. The results are presented in Table I.

First consider the mean of the point estimates obtained for each method in each simulation design. We observed that the estimates $\mathcal{R}_{0,n}$, $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$ were identical in the uncensored cases, corresponding to the cases where the rate of unknown t_0 -status individuals was null. In addition, we observed that $\mathcal{R}_{1,n} < 1$ in every case, and that the bias magnitude depended upon

the "prevalence" $1/\lambda$, independently of the rate of unknown t_0 -status individuals. Finally, the error made when using $\mathcal{R}_{0,n}$ was all the higher as this rate increased (as expected again). All these observations confirmed the assertions presented in Section 2. The correcting terms presented in Table II made these observations even clearer and supported the approximation stated in (11). Furthermore, the estimates $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$ gave very similar values, which were close to the true value 1. These first results confirmed the fact that $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$ were better estimates of the \mathcal{E}/\mathcal{O} ratio than $\mathcal{R}_{0,n}$ and $\mathcal{R}_{1,n}$, and then that the use of the latter two estimators should be avoided.

Considering in more detail $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$, we saw that the means of the $\mathcal{R}_{3,n}$'s were slightly closer to 1 than those of the $\mathcal{R}_{2,n}$'s. Moreover, by comparing the width and the covering probability of the corresponding confidence interval, $\mathcal{R}_{3,n}$ appeared to be more precise than $\mathcal{R}_{2,n}$, with narrower but still more accurate confidence intervals. Therefore, from this simple simulation study, the estimate $\mathcal{R}_{3,n}$ turned out to be the most advisable one.

Note that the precision of $\mathcal{R}_{3,n}$ (as well as that of $\mathcal{R}_{2,n}$) was closely related to the prevalence $1/\lambda$: the higher the prevalence, the more precise the estimates.

4. CASE STUDY : THE EVALUATION OF AN EXISTING BREAST CANCER PREDICTION TOOL ON THE E3N COHORT

E3N (Etude Epidémiologique des femmes de l'Education Nationale) is the French component of the EPIC (European Prospective Investigation into Cancer and nutrition) prospective study and has been thoroughly described elsewhere [6]. All participants are women belonging to the Mutuelle Générale de l'Education Nationale (MGEN), a health insurance scheme primarily covering teachers, teacher's spouses, and employees of the National Education System. Since June 1990, after having given informed consent, 98,995 women have been asked at approximately 24-month intervals to complete self-administered questionnaires, which include a variety of lifestyle characteristics. After the exclusion of the prevalent cases of cancer ($n=6,999$) and women who had never menstruated ($n = 28$), the cohort includes 91,968 observations (with 3,467 cases of invasive breast cancer).

Rosner and Colditz models proposed two breast cancer risk prediction models according to which incidence of breast cancer at age a (I_a) is proportional to the number of breast cell divisions accumulated throughout life up to age a [16], [2]. The rate of breast cancer cell division at age a' is supposed to be dependent on risk factors that are relevant at age a' . Rosner and Colditz thus expressed the log incidence rate of breast cancer as a linear function of the cumulative effect of individual breast cancer risk factors. In a first attempt [16], in addition to age (a), only reproductive factors were considered, namely, age at menarche (a_0), menopausal status (m), age at menopause (a_m), parity s , age at first birth (a_1), and a variable b , called *birth index* and defined as $b = \sum_{i=1}^s (a^* - a_i)b_{i,a}$, where a_i is the age at i th birth, $a^* = \min(a, a_m)$ and $b_{i,a} = 1$ if parity is greater than i at age a , 0 otherwise. Defining b_1 as 1 if $s \geq 1$, 0 otherwise, the *RCM* was specified as

$$\begin{aligned} \log I_a = & \alpha + \beta_0 a_0 + \beta_1 (a^* - a_0) + \beta_2 (a - a_m)m \\ & + \beta_3 (a_1 - a_0)b_1 + \beta_4 b + \beta_5 b(a - a_m)m. \end{aligned} \quad (14)$$

The values of the parameters $\alpha, \beta_1, \dots, \beta_5$ estimated in [16] are recalled for convenience in Table III.

Rosner and Colditz later developed a model including more factors [2]; an evaluation study of the two versions can be found in Rockhill et al. [15]. We chose to evaluate the first version (*RCM*) as some of the variables involved in the extended one were not available in the E3N study (BMI at menarche, for instance). Moreover, our aim was to measure the respective performances of the methods presented in Section 2 rather than to evaluate the best published model.

To compute the t -year risk (where t can take the value t_0 or z_i depending on the method to be used to evaluate the *RCM*), we proceeded as in Rockhill et al.'s evaluation study [15]: once we obtained, from (14), the log incidence rates for each year for each woman, we exponentiated each one to get an incidence rate r_j , $j = 1, \dots, t$, for each year during the t -year period; then, the t -year risk was computed as $1 - \exp(-[r_1 + \dots + r_t])$. We chose $t_0 = 10$ years. In addition, we performed the evaluation on three groups:

- the whole sample ($n = 91,968$);

- Postmeno. Group 1, comprised of women who were at inclusion ($n = 36,603$);
- Postmeno. 2, comprised of Postmeno. Group 1 plus the women who went through the menopause during the study (these women entered this group at the time of their menopause) ($n = 82,402$).

For the whole sample ($n = 91,968$), the rate of unknown t_0 -status individuals was 12% ($n_{ks} = 80,883$), and the Kaplan-Meier estimate of the unconditional risk of disease was 3.21%. For Postmeno. Group 1 ($n = 36,603$), the rate of unknown t_0 -status individuals was 12.5% ($n_{ks} = 32,027$), and the Kaplan-Meier estimate of the unconditional risk of disease was 3.39%. For Postmeno. Group 2 ($n = 82,402$), the rate of unknown t_0 -status individuals was 51.5% ($n_{ks} = 39,931$), and the Kaplan-Meier estimate of the unconditional risk of disease was 3.60%. The results presented in Table IV were consistent with our previous explanations. The estimates $\mathcal{R}_{2,n}$ and $\mathcal{R}_{3,n}$ gave similar results, whereas $\mathcal{R}_{1,n}$ and especially $\mathcal{R}_{0,n}$ were slightly different and conceivably biased. Moreover, $\mathcal{R}_{3,n}$ was more precise than $\mathcal{R}_{2,n}$. Note that the bias magnitude of $\mathcal{R}_{0,n}$ was of the same order as that expected in view of the results of the simulation study. In fact, for the whole sample and Postmeno. Group 2, the rate of unknown t_0 -status individuals was about 12 %. In our simulation study, we observed that $\tilde{\mathcal{C}}_0(t_0) \simeq 1.055$ for 10 % of unknown t_0 -status individuals. Here, we had $\mathcal{C}_0(t_0) = 1.065$ and $\mathcal{C}_0(t_0) = 1.074$ on the whole sample and Postmeno. Group 1 respectively (on Postmeno. Group 2, we had $\mathcal{C}_0(t_0) = 1.43$, but this feature could not be compared with our simulated results, since the rate of unknown t_0 -status individuals reached 51.5% for this group). However, the bias magnitude of $\mathcal{R}_{1,n}$ was slightly less important than what could have been expected from our simulation study. Indeed, the prevalence of the disease was about 1/300 per year (around 1/30 over 10 years), and we calculated $\mathcal{C}_0(t_0) \simeq 1.01$, while 1.02 was expected. This highlights the fact that the distribution of Y plays an important role with respect to the bias of $\mathcal{R}_{1,n}$. In fact, this bias is larger for a uniform distribution than, for instance, an exponential one, where cases are likely to occur later (and in which case, the terms $e_i(z_i)$ are likely to be closer to $e_i(t_0)$).

Note that the *RCM* appeared to slightly underestimate the breast cancer risk in the whole

E3N population. This underestimation was wider for the postmenopausal groups, especially on Postmeno. Group 2. The main reason might be that *RCM* does not take hormone replacement therapy (HRT) use into account. HRT is known to increase the risk of cancer [5], [6]. Moreover, the use of HRT is more and more frequent in the E3N population as well as in the general population: this means that, overall, the use of HRT is more frequent in Postmeno. Group 2 than in Postmeno. Group 1. Therefore, this could explain (at least partly) the wider underestimation observed on Postmeno. Group 2.

5. DISCUSSION

We have presented and compared four methods aimed at evaluating the calibration of disease risk prediction tools. It was shown that the estimates $\mathcal{R}_{3,n}$ and $\mathcal{R}_{2,n}$ should be preferred to $\mathcal{R}_{0,n}$ and $\mathcal{R}_{1,n}$, the latter two being biased in most situations. The estimator $\mathcal{R}_{3,n}$ appeared to be more precise than $\mathcal{R}_{2,n}$ on simulated data. In addition, the unbiasedness of $\mathcal{R}_{2,n}$ was not theoretically established here, and its applicability was shown to be limited (in particular, it should not be used when calibration has to be adjusted for percentiles of predicted risks).

Some other more sophisticated criteria (such as Hosmer and Lomeshow [11] *goodness-of-fit* statistics) may also be retained to evaluate the calibration. Here, we focused on the so-called *E/O* ratio, but the problems arising in this simple case of course still arise when more sophisticated criteria are used, and we recommend the use of the Kaplan-Meier estimate to estimate the "O" terms involved in the Hosmer-Lomeshow statistic. If this is done, however, we also recommend either checking the χ^2 distribution of the resulting statistic or using bootstrap techniques to derive the associated p-value.

The problem of individuals who dropped out before t_0 years of follow-up still arises when evaluating the discrimination of a t_0 -year risk score. It has been shown that the concordance statistic is biased when estimated only on the known t_0 -status group, and an unbiased estimate has been proposed when the underlying model is a Cox proportional hazard model with time under study as the time scale [10]. In other cases, no unbiased estimates have ever been

proposed. An alternate approach is to compute the *Observed Relative Risk (ORR)*. To do this, individuals have to be sorted by predicted t_0 -year risks. Then, the *ORR* is simply the ratio of the number of observed cases in the top decile (or quintile) of predicted t_0 -year risks to the number of observed cases in the bottom decile (or quintile). Obviously, since observed numbers of cases are generally not at the statistician's disposal, Kaplan-Meier estimates (and bootstrap confidence intervals) are required in this setting too.

As a conclusion, we strongly recommend the use of $\mathcal{R}_{3,n}$ as an estimate of the \mathcal{E}/\mathcal{O} , even if it is not the most commonly used estimate in the evaluation of calibration literature (especially in the breast cancer field).

6. APPENDIX

6.1. Proof of (11)

Our aim is first to prove (11), which is recalled in (15) below for convenience,

$$\mathcal{C}_1(t_0) \approx \frac{F_{n_{ks}}(t_0)}{K_n(t_0)}. \quad (15)$$

First note that

$$\frac{E_{\mathbb{S}_n}}{O_{\mathbb{S}_n}} = \frac{(E_{\mathbb{S}_{n,uks}} + E_{\mathbb{S}_{n,ks}})}{O_{\mathbb{S}_{n,ks}}} \frac{O_{\mathbb{S}_{n,ks}}}{O_{\mathbb{S}_n}} = \frac{E_{\mathbb{S}_{n,ks}}}{O_{\mathbb{S}_{n,ks}}} \left(1 + \frac{E_{\mathbb{S}_{n,uks}}}{E_{\mathbb{S}_{n,ks}}} \right) \frac{O_{\mathbb{S}_{n,ks}}}{O_{\mathbb{S}_n}},$$

where $O_{\mathbb{S}_{n,uks}}$ (resp. $E_{\mathbb{S}_{n,uks}}$) is the observed (resp. expected) number of cases on $\mathbb{S}_{n,uks}$.

Keeping in mind that $O_{\mathbb{S}_{n,ks}} = n_{ks}F_{n_{ks}}(t_0)$, $\widehat{O}_{\mathbb{S}_n} = nK_n(t_0)$ and $n = n_{ks} + n_{uks}$, it is straightforward that

$$\frac{E_{\mathbb{S}}}{\widehat{O}_{\mathbb{S},n}} = \frac{E_{\mathbb{S}_{n,ks}}}{O_{\mathbb{S}_{n,ks}}} \left(\frac{1 + E_{\mathbb{S}_{n,uks}}/E_{\mathbb{S}_{n,ks}}}{1 + n_{uks}/n_{ks}} \right) \frac{F_{n_{ks}}(t_0)}{K_n(t_0)}.$$

Next, introduce the following assumption:

(H) The censoring process is independent from the covariates.

Remark 1. *The condition (H) ensures that the distribution of the covariates is the same on $\mathbb{S}_{n,uks}$ and $\mathbb{S}_{n,ks}$ (and then on \mathbb{S}_n).*

Under (H) , with $\hat{e}_n = E_{\mathbb{S}_n}/n$,

$$\frac{E_{\mathbb{S}_n, \text{uks}}}{E_{\mathbb{S}_n, \text{ks}}} \simeq \frac{\hat{e}_n n_{\text{uks}}}{\hat{e}_n n_{\text{ks}}} = \frac{n_{\text{uks}}}{n_{\text{ks}}},$$

in such a way that

$$\frac{E_{\mathbb{S}_n}}{\widehat{O}_{\mathbb{S}_n}} \simeq \frac{E_{\mathbb{S}_n, \text{ks}}}{O_{\mathbb{S}_n, \text{ks}}} \frac{F_{n_{\text{ks}}}(t_0)}{K_n(t_0)}. \quad (16)$$

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Table I. Results of the simulation studies. The mean of the estimate of the \mathcal{E}/\mathcal{O} ratio, the mean of the width of the corresponding confidence interval and the proportion of these intervals including the value 1 are given respectively for each of the four methods in each of the 12 simulation designs. Means were obtained from 1,000 independent samples.

Rate of UKSI [‡]	Observed Cases	Method M_0			Method M_1			Method M_2			Method M_3		
<i>Case 1 : $\lambda = 100$</i>													
0	2,000	1.000	0.088	0.967	0.950	0.083	0.374	1.000	0.088	0.967	1.000	0.083	0.957
5%	1,947	0.976	0.087	0.809	0.951	0.085	0.406	1.001	0.089	0.955	1.001	0.084	0.946
10%	1,895	0.950	0.086	0.391	0.951	0.086	0.410	1.002	0.090	0.967	1.001	0.086	0.961
20%	1,787	0.893	0.083	0.003	0.953	0.088	0.462	1.004	0.093	0.963	1.001	0.088	0.951
<i>Case 2 : $\lambda = 200$</i>													
0	1,001	1.000	0.124	0.954	0.975	0.121	0.876	1.000	0.124	0.954	1.000	0.121	0.949
5%	973	0.976	0.123	0.891	0.978	0.123	0.891	1.003	0.126	0.960	1.002	0.123	0.953
10%	948	0.949	0.121	0.620	0.976	0.124	0.898	1.002	0.128	0.958	1.001	0.124	0.956
20%	896	0.890	0.117	0.066	0.977	0.128	0.887	1.003	0.132	0.959	1.001	0.128	0.955
<i>Case 3 : $\lambda = 400$</i>													
0	500	1.002	0.176	0.950	0.990	0.174	0.931	1.002	0.176	0.950	1.002	0.174	0.950
5%	488	0.976	0.174	0.907	0.989	0.176	0.939	1.002	0.178	0.964	1.002	0.181	0.960
10%	475	0.948	0.171	0.783	0.989	0.178	0.942	1.001	0.181	0.968	1.001	0.178	0.964
20%	448	0.893	0.166	0.313	0.992	0.184	0.965	1.005	0.187	0.968	1.004	0.185	0.966

[‡] Unknown t_0 -status individuals.

Table II. Results of the simulation studies showing the mean of the correction terms. Means were obtained from 1,000 independent samples.

Rate of UKSI [‡]	Correction term $\tilde{\mathcal{C}}_0(t_0)^{\dagger}$	Correction term $\mathcal{C}_1(t_0)^*$
<i>Case 1 : $\lambda = 100$</i>		
0	1.000	1.053
5%	1.025	1.053
10%	1.053	1.054
20%	1.120	1.055
<i>Case 2 : $\lambda = 200$</i>		
0	1.000	1.026
5%	1.026	1.026
10%	1.055	1.026
20%	1.124	1.027
<i>Case 3 : $\lambda = 400$</i>		
0	1.000	1.013
5%	1.026	1.013
10%	1.055	1.013
20%	1.125	1.013

[‡] Unknown t_0 -status individuals.

[†] $\tilde{\mathcal{C}}_0(t_0) = F_{n_{\text{ks}}}(t_0)/K_n(t_0)$.

^{*} $\mathcal{C}_1(t_0) = \mathcal{R}_{2,n}/\mathcal{R}_{1,n}$.

Table III. Coefficients of the first Rosner and Colditz model (*RCM*).

Parameter	Regression coefficient	SE*
α (intercept)	-9.687	0.265
β_0 (age at menarche)	0.048	0.016
β_1 (min[age, age at menopause] – age at menarche)	0.081	0.004
β_2 (age – age at menopause), for menopausal women	0.050	0.005
β_3 (age at first birth – age at menarche)	0.013	0.004
β_4 (birth index)	-0.0036	0.0009
β_5 (birth index \times [age – age at menopause]), for menopausal women	-0.00020	0.00012

*SE: standard error.

Table IV. Evaluation of the calibration of the Rosner and Colditz 10-year risk of breast cancer prediction tool. Results from the E3N cohort.

Population for validation	Rate of UKSI [‡]	Observed Cases	Method M_0 [CI*]	Method M_1 [CI*]	Method M_2 [CI*]	Method M_3 [CI*]
Whole sample	12.1%	2,765	0.889 [0.839-0.941]	0.932 [0.880-0.987]	0.940 [0.887-0.996]	0.947 [0.912-0.982]
Postmeno. Group 1 [†]	12.5%	1,160	0.635 [0.600-0.673]	0.672 [0.634-0.711]	0.678 [0.640-0.718]	0.682 [0.644-0.721]
Postmeno. Group 2 [‡]	51.5%	2,115	0.417 [0.394-0.442]	0.591 [0.558-0.626]	0.597 [0.564-0.633]	0.595 [0.569-0.620]

* CI : Confidence intervals.

[‡] Unknown t_0 -status individuals.[†] Postmenopausal women at inclusion.[‡] Postmenopausal women during follow-up.